DETAILED ACTION

Receipt of applicants' amendments and remarks submitted July 25, 2008 is acknowledged.

Claim Rejections 35 U.S.C. 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 20-22, 24,49, 50,55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waldrep et al. (US 5,958,378), Hauer et al. (US 5342625), and Fuji et al. (US 6,197,829), in view of Adjei et al. (US 5,635,161), Knight et al. (5,049,388), Gordon et al. (US 6,657,893) and Iacono et al. (Am J, Respir. Crit. Care Med. Vol. 155, pp 1690-1698, 1997, IDS), and in further view of Stanford et al. (EP 0372 541).

3. Waldrep et al. Hauer et al. and Fuji et al. teaches that cyclosporine are old and well known in combination with various pharmaceutical carriers and excipients in various dosage forms, particularly, aerosol dosage form. These medicaments are taught as useful as immunosuppressant for treating or preventing graft rejections, inflammation and other immunological mediated conditions such as graft rejections of lung, heart, and other organs, asthma, autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosis. Specific liposome aerosol dosages are disclosed. The aerosol dosage may be either is solution or in powder forms. See, particularly, the abstract, col. 4, line 22 to col. 5, 64, the examples, col. 13, lines 3-60, and the claims in Waldrep et al; col. 1, lines 43-51, col. 25, lines 50-58 in Hauer et

al.; and, column 7, lines 40 to col. 8, lines 59, and the claims in Fuji et al. Cyclosporine is particularly known to be used with other immunosuppressant for treatment of those disorders. See, the claims in Fuji.

4. Waldrep et al. Hauer et al. and Fuji et al. as a whole do not teach expressly the various dosage forms, or the dosage levels herein claimed, or the particular time of administration as herein claimed.

However, Adjei et al. teaches that pulmonary delivery of peptide and protein biotherapeutics, such as cyclosporine, by aerosol is well known in the art. Both suspension (solid particle) and solution aerosol formulas are known in the art. propellants are normally used with the aerosol composition. See, particularly, Col. 1, lines 15 to col. 2, line 65, and the examples. Knight et al. teaches that cyclosporine aerosol dosage may be in the form of powder. See, particularly, example 2 therein. Gordon et al. disclosed that dry powder is a well-known form for pulmonary aerosol drug delivery. See, particularly, col. 1, lines 15-67, and the claims. Iacono et al. teaches a cyclosporine composition for aerosol delivery consisting of cyclosporine, a solvent and a propellant and the method of using the same for treating lung graft rejections. See, the whole article, particularly, page 1691, col. 2, the paragraph subtitled "Drug preparation, aerosol generation, and therapy."

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to treating the patients of organ transplantation, e.g., lung transplantation prior to the development of symptoms associated the transplant rejection with the aerosol composition comprising cyclosporine and another immunosuppressant. Stanford et al. teaches that immunosuppressive agents are known to be useful for reducing the

frequency of acute transplant rejections. See, particularly, the abstract, page 3, lines 35-40 and fig. 6.

5. A person of ordinary skill in the art would have been motivated to treating the patients of organ transplantation, e.g., lung transplantation prior to the development of symptoms associated the transplant rejection with the aerosol composition comprising cyclosporine and another immunosuppressant, because cyclosporine are known to be useful for organ transplantation patients, and are particularly known to be delivered through pulmonary delivery. Further, the cited prior art as a whole teach various aerosol formulation of cyclosporine, encapsulated, or un-encapsulated as an improvement over simple aerosol employment of powdered active ingredient, and the aerosol cyclosporine as useful for an anti-inflammation, anti-rejection medicaments. The skilled artisan would have possessed all conventional administration regimens, and seen the selection of one or another as the simple selection from among obvious alternatives. Further, optimization of a result effective parameter, e.g., effective amount of a therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. As to the recitation of "chronic refractory" in the claims, it is noted that a method known for preventing transplantation rejections would reasonably expected to prevent the development of rejections, either chronic or acute.

6. The instant claims are directed to affecting a biochemical pathway with an old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (transplantation rejection) for the compounds, e.g., cyclosporine, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re

Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various functions. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Response to the Arguments

Applicants' amendments, remarks and exhibits submitted July 25, 2008 have been fully considered, but are not persuasive.

Applicant contends that the cited references, or prior art as a whole, do not teach or suggest administering inhaled cyclosporine to a lung transplantation patient prior to the development of refractory rejection, to inhibit chronic rejection.

Applicant also asserts that one of ordinary skill in the art would have not been motivated to employ aerosolized cyclosporine as it is inconvenient and costly, citing inventor's recently publication.

Applicant further argues that Acute rejection and chronic rejections are pathologically distinct from each other, and therefore, there is no reasonable expectation of success for preventing chronic rejection based on a teaching of preventing acute rejections.

The arguments are not persuasive for at least the following reasons:

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claimed invention is a therapeutical method, like any other therapeutical method, the limitations in the claims are:

A) Patient population: Patients who had lung transplantation who do not have symptoms of rejections. Note "for inhibiting chronic graft rejection" is not seen to further limit the patient population as the application, or the prior art, disclose any means to identify those lung transplant patients who will develop chronic graft rejection, and those who will not develop chronic graft rejection.

B) Active ingredient (s): Cyclosporine, and other immunosuppressive agent and/or anti-inflammatory agent (in dependent claim).

C) Step(s) for administering the active agent(s): Route: not defined, but lung delivery is within the scope; Form: aerosolized composition, solution or powder (dependent claims); Timing: prior to development of refractory graft rejection, within 10, or 31 day (dependent claims); amounts: effective amounts, 15 to 30 mg/a lung (dependent claim,).

The scope and content of the prior art: Prior art teaches the treatment of lung transplantation patient with cyclosporine. Prior art teach prevention of rejection, therefore teaches administration of cyclosporine before the development of any symptom of rejections.

Therefore, the prior art teach the employ the same active ingredient(cyclosporine) for the same patient population (patients just have lung transplantation and have no symptoms of rejection). The particular dosage forms herein employed are also known in the art.

Further, optimization of a result effective parameter, e.g., effective amount of a therapeutical agent, or the timing for a preventive purpose, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215.

Therefore, a prima facie case of obviousness is established.

The arguments that one of ordinary skill in the art would have not been motivated to employ aerosolized cyclosporine as it is inconvenient and costly is not persuasive as the cited references, or other references on the record have shown that aerosolized cyclosporine has been used in the art. See, for example, exhibit A, page 384, the right columns.

8. In response to applicant's argument that the cited reference do not teach expressly for inhibiting chronic graft rejection, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shengjun Wang/
Primary Examiner, Art Unit 1617